DRUG INTERACTIONS (Updated January 10, 2011)

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral (ARV) regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. In addition, the potential for drug interactions should be assessed when any new drug, including over-the-counter agents, is added to an existing ARV combination. **Tables 14–16b** list significant drug interactions with different ARV agents and suggested recommendations on contraindications, dose modifications, and alternative agents.

Protease Inhibitors (PIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Most drug interactions with ARV drugs are mediated through inhibition or induction of hepatic drug metabolism *[1]*. All PIs and NNRTIs are metabolized in the liver by the cytochrome P (CYP) 450 system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs or NNRTIs is extensive and is continuously expanding. Some examples of these drugs include medications that are commonly prescribed in HIV-infected patients for non-HIV medical conditions, such as lipid-lowering agents (e.g., statins), benzodiazepines, calcium channel blockers, immunosuppressants (e.g., cyclosporine and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (e.g., sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, and methadone. Herbal products, such as St. John's wort, can also cause interactions that risk adverse clinical effects.

All PIs are substrates of CYP3A4, so their metabolic rates may be altered in the presence of CYP inducers or inhibitors. Some PIs may also be inducers or inhibitors of other CYP isoenzymes and of P-glycoprotein or other transporters in the gut and elsewhere. Tipranavir (TPV), for example, is a potent inducer of CYP3A4 and P-glycoprotein. The net effect of tipranavir/ritonavir (TPV/r) on CYP3A *in vivo* appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are likely to be increased if given with TPV/r. The net effect of TPV/r on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir (SQV), amprenavir (APV), and lopinavir (LPV) concentrations have been observed *in vivo* when given with TPV/r.

The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine [NVP]), an inhibitor (delavirdine [DLV]), or a mixed inducer and inhibitor (efavirenz [EFV]). Etravirine (ETR) is a substrate of CYPs 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4 and an inhibitor of CYPs 2C9 and 2C19. Thus, these ARV agents can interact with each other in multiple ways and with other drugs commonly prescribed for other concomitant diseases.

The use of a CYP3A4 substrate that has a narrow margin of safety in the presence of a potent CYP3A4 inhibitor may lead to markedly prolonged elimination half-life ($t_{1/2}$) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities, may be warranted.

The inhibitory effect of ritonavir (RTV), however, can be beneficial when added to a PI, such as atazanavir (ATV), fosamprenavir (FPV), or indinavir (IDV) *[2]*. The PIs darunavir (DRV), LPV, SQV, and TPV require coadministration with RTV. Lower than therapeutic doses of RTV (100 to 400 mg per day) are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the half-life of the active PIs *[3]*. The higher C_{min} allows for a greater C_{min}: inhibitory concentration (IC_{50}) ratio, which reduces the chance for development of drug resistance as a result of suboptimal drug exposure; the longer half-life allows for less frequent dosing, which may enhance medication adherence.

Coadministration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the ARV agents. These drug combinations should be avoided if alternative agents can be used. If this is not possible, close monitoring of plasma HIV RNA, with or without ARV dosage adjustment and therapeutic drug monitoring (TDM), may be warranted. For example, the rifamycins (i.e., rifampin and, to a lesser extent, rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[4-5]*. Because rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of tuberculosis (TB) when it is used with a PI-based regimen, despite wider experience with rifampin use *[6]*. **Tables 15a and 15b** list dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers with PIs and NNRTIs.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include increases in intracellular drug levels and toxicities when didanosine (ddI) is used in combination with hydroxyurea *[7-8]* or ribavirin *[9]*, additive bone marrow suppressive effects of zidovudine (ZDV) and ganciclovir *[10]*, and antagonism of intracellular phosphorylation with the combination of ZDV and stavudine (d4T) *[11]*. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Examples of such interactions include increases of ddI concentration in the presence of tenofovir (TDF) *[12]* and decreases in ATV concentration when ATV is coadministered with TDF *[13]*. **Table 15c** lists significant interactions with NRTIs.

CCR5 Antagonist

Maraviroc (MVC), the first Food and Drug Administration (FDA)-approved CCR5 antagonist, is a substrate of CYP3A enzymes and P-glycoprotein. As a consequence, the concentrations of MVC can be significantly increased in the presence of strong CYP3A inhibitors (such as RTV and other PIs, except for TPV/r) and are reduced when used with CYP3A inducers (such as EFV or rifampin). Dose adjustment is necessary when MVC is used in combination with these agents. (See **Table 16b** or **Appendix B, Table 6** for dosage recommendations.) MVC is neither an inducer nor an inhibitor of the CYP3A system and does not alter the pharmacokinetics of the drugs evaluated in interaction studies to date.

Integrase Inhibitor

Raltegravir (RAL), an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation that is mediated by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of RAL *[14]*. (See **Table 15e** for dosage recommendations.) Other inducers of UGT1A1, such as EFV and TPV/r, can also reduce RAL concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

Fusion Inhibitor

The fusion inhibitor enfuvirtide (T-20) is a 36–amino acid peptide that does not enter human cells. It is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction has been identified with T-20 to date.

References

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Table 14. Drugs That Should Not Be Used With Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, or CCR5 Antagonist (Updated October 14, 2011)

This table lists only drugs that should not be coadministered at any dose and regardless of RTV boosting. See Tables 15 and 16 for more detailed pharmacokinetic interaction data and dosage adjustments.

Drug Categories										
Antiretroviral Agents[1,2]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Antiretroviral Agents**	**Others**
ATV +/− RTV	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/− RTV	flecainide propafenone	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
LPV/r	none	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
RTV	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin sildenafil for PAH
SQV/r	amiodarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine	cisapride[5]	pimozide	midazolam[6] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supplements	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
EFV	none	none	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[3]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbamazepine phenobarbital phenytoin clopidogrel
NVP	none	none	rifapentine[3]	none	none	none	none	St. John's wort	ATV +/− RTV other NNRTIs	ketoconazole
RPV	none	none	rifabutin rifampin rifapentine	proton pump inhibitors	none	none	none	St. John's wort	Other NNRTIs	carbamazepine oxcarbazepine phenobarbital phenytoin
MVC	none	none	rifapentine[3]	none	none	none	none	St. John's wort	none	none

1 DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV-, IDV-, and NFV-related drug interactions.

2 Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

3 HIV-infected patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

4 A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.

5 The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

6 Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:

Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with DRV/r, see Table 15a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.

Rifampin: Rifabutin (with dosage adjustment, see Tables 15a and 15b)

Midazolam, triazolam: temazepam, lorazepam, oxazepam

Key to Abbreviations: ATV +/- RTV = atazanavir +/- ritonavir, DLV = delavirdine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV +/- RTV = fosamprenavir +/- ritonavir, HIV = human immunodeficiency virus, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PAH = pulmonary arterial hypertension, PI = protease inhibitor, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TB = tuberculosis, TPV/r = tipranavir/ritonavir

Table 15a. Drug Interactions between PIs* and Other Drugs (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

This table provides information relating to pharmacokinetic interactions between PIs and non-ARV drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among ARV agents and for dosing recommendations, refer to **Table 16a**.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/− RTV	↓ ATV expected when given simultaneously	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C_{min}	Give FPV simultaneously with or at least 2 hours before or 1 hour after antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H_2 receptor antagonists	**RTV-boosted PIs**		
	ATV/r	↓ ATV	H_2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	
	PIs without RTV		
	ATV	↓ ATV	H_2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naïve patients. Give ATV at least 2 hours before and at least 10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	Give FPV at least 2 hours before H_2 receptor antagonist if concomitant use is necessary. Consider boosting with RTV.
Proton pump inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naïve patients. PPIs should be administered at least 12 hours prior to ATV/r. **PPIs are not recommended in PI-experienced patients**.
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose with TPV/r.
	FPV +/– RTV, LPV/r	No significant effect	
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
Anticoagulants			
Warfarin	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, SQV/r, TPV/r	↑ or ↓ warfarin possible DRV/r ↓ S-warfarin AUC 21%	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and response. Monitor for LPV-related toxicities.
Antidepressants			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Paroxetine	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 58%	
Sertraline	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
Trazodone	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not coadminister.**
Tricyclic antidepressants (TCAs) (amitriptyline, desipramine, imipramine, nortriptyline)	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Antifungals			
Fluconazole	**RTV-boosted PIs**		
	ATV/r	No significant effect	

	SQV/r	No data with RTV boosting SQV (1,200 mg TID) AUC ↑ 50%	
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
Itraconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dosing is guided by drug levels.
	LPV/r	↑ itraconazole	Consider not exceeding 200 mg itraconazole daily or monitor itraconazole level.
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV		
	ATV, FPV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
Voriconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
Anti-mycobacterials			
Clarithromycin	ATV +/− RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% and ↓ active metabolite 97% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities. Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dose adjustment
Rifabutin	**RTV-boosted PIs**		
	ATV +/– RTV	rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300 mg daily alone	Rifabutin 150 mg every other day or three times a week. Some experts recommend rifabutin 150 mg daily or 300 mg three times a week. Monitor for antimycobacterial activity. Therapeutic drug monitoring for rifabutin is recommended. Rifabutin 150 mg three times a week in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Pharmacokinetic data reported in this table are results from healthy volunteer studies.
	DRV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300 mg once daily alone	
	FPV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin 300 mg once daily alone	

	LPV/r	rifabutin (150 mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300 mg daily alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
Rifampin	All PIs	↓ PI >75% approximately	**Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity.
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV 200 mg BID for two days ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and C_{max} 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg BID ↑ triazolam half-life 1,200% and AUC 2,000%	**Do not coadminister triazolam and PIs.**
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and ATV without RTV.** In patients on a PI (other than unboosted ATV) >10 days: start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted ATV): stop bosentan ≥36 hours prior to PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV 200 mg BID ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine calcium channel blockers (CCBs)	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
Diltiazem	ATV +/– RTV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV +/– RTV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.

Corticosteroids			
Dexamethasone	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Fluticasone (inhaled or intranasal)	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Coadministration can result in adrenal insufficiency, including Cushing's syndrome. **Do not coadminister unless potential benefit outweighs risk of systemic corticosteroid adverse effects.**
Prednisone	LPV/r	↑ prednisolone AUC 31%	No dosage adjustment necessary.
Herbal Products			
St. John's wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	**RTV-boosted PIs**		
	ATV/r	↓ ethinyl estradiol ↑ norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional method.
	LPV/r	ethinyl estradiol AUC↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternate method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; LPV/r ↑ atorvastatin AUC 488%; SQV/r ↑ atorvastatin AUC 79%; TPV/r ↑ atorvastatin AUC 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	ATV	pitavastatin AUC ↑ 31%; C_{max} ↑ 60% ATV: no significant effect	No dosage adjustment needed for ATV without RTV.
	All RTV-boosted PIs	↑ pitavastatin possible	**Do not coadminister** due to possible increase in pitavastatin concentration and increased risk of rhabdomyolitis.

Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
	SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary
Rosuvastatin	ATV/r	rosuvastatin AUC ↑ 213% and C_{max} ↑ 600%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	DRV/r, FPV +/- RTV, SQV/r	↑ rosuvastatin possible	
	LPV/r	rosuvastatin AUC ↑ 108% and C_{max} ↑ 366%	
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3,059%	**Contraindicated. Do not coadminister**.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.** Norbuprenorphine is an active metabolite of buprenorphine.
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary. Norbuprenorphine is an active metabolite of buprenorphine.
	DRV/r	buprenorphine: no significant effect norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment necessary. Clinical monitoring is recommended. Norbuprenorphine is an active metabolite of buprenorphine.
	LPV/r	No significant effect	No dose adjustment necessary
	TPV/r	buprenorphine: no significant effect norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19–40%	Consider monitoring TPV level. Norbuprenorphine is an active metabolite of buprenorphine.
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r ↓ R-methadone AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100 mg BID ↓ R-methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opioid withdrawal and increase methadone dose as clinically indicated. (R-methadone is the active form of methadone.)
	PIs without RTV		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar. (R-methadone is the active form of methadone.)
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	All PIs	DRV/r + sildenafil 25 mg similar to sildenafil 100mg alone; RTV 500 mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	<u>For treatment of erectile dysfunction</u> Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. <u>For treatment of pulmonary arterial hypertension</u> **Contraindicated**

Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124%; TPV/r (1st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	<u>For treatment of erectile dysfunction</u> Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. <u>For treatment of pulmonary arterial hypertension</u> *In patients on a PI >7 days*: Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI*: Stop tadalafil <u>≥</u>24 hours prior to PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Miscellaneous Interactions			
All PIs	Colchicine	All PIs	<u>For treatment of gout flares</u> Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV*: 1.2 mg x 1 dose and no repeat dose for at least 3 days <u>For prophylaxis of gout flares</u> Colchicine 0.3 mg once daily or every other day *With FPV without RTV*: colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily <u>For treatment of familial Mediterranean fever</u> Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV*: Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
	Salmeterol	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia.
ATV/r LPV/r	Atovaquone/proguanil	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Acronyms: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir + ritonavir, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, CNS = central nervous system, CrCl = creatinine clearance, CYP = cytochrome P, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, FDA = Food and Drug Administration, FPV = fosamprenavir (FPV is a prodrug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TB = tuberculosis, TCA = tricyclic antidepressant, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid.

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors* and Other Drugs (Updated October 14, 2011)

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, refer to **Table 16b**.

*DLV is not included in this table. Please refer to the FDA package insert for information regarding DLV drug interactions.

Concomitant Drug Class/Name	NNRTI[1]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H_2-Receptor Antagonists	RPV	↓ RPV	Give H_2-receptor antagonists at least 12 hours before or at least 4 hours after RPV.
Proton Pump Inhibitors (PPI)	RPV	↓ RPV	**Contraindicated. Do not coadminister.**
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses.
	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Antifungals			
Fluconazole	EFV	No significant effect	
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with fluconazole.)
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Consider monitoring NNRTI and itraconazole levels and antifungal response.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150mg/day reduces ketoconazole exposure; no data on interaction with itraconazole.)
Posaconazole	EFV	posaconazole AUC ↓ 50% ↔ EFV	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with posaconazole.)
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.

Concomitant Drug Class/Name	NNRTI[1]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with voriconazole.)
Antimycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% OH-clarithromycin AUC ↑ 21% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31% OH-clarithromycin AUC ↑ 42%	Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	rifabutin ↓ 38%	Dose: rifabutin 450–600 mg once daily or 600 mg three times a week if EFV is not coadministered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: rifabutin 300 mg once daily **if** ETR is not coadministered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	RPV AUC ↓ 46%	**Contraindicated. Do not coadminister.**
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Some clinicians suggest EFV 800 mg dose in patients who weigh more than 60 kg.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not coadminister.**
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C_{max} ↑ 16%, AUC no significant effect	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem	EFV	diltiazem AUC ↓ 69%	Titrate diltiazem dose based on clinical response.
	NVP	↓ diltiazem possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Herbal Products			
St. John's wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Do not coadminister.**

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
		depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary.
	RPV	ethinyl estradiol AUC ↑ 14% norethindrone: no significant change	No dosage adjustment necessary.
Levonorgestrel	EFV	levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	atorvastatin AUC ↓ 32%–43% with EFV, ETR	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV, ETR, NVP	No data	No dosage recommendation.
Pravastatin **Rosuvastatin**	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected with either pravastatin or rosuvastatin	No dosage adjustment necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EFV	buprenorphine AUC ↓ 50% norbuprenorphine AUC ↓ 71%	No withdrawal symptoms reported. No dosage adjustment recommended, but monitor for withdrawal symptoms.
	NVP	No significant effect	No dosage adjustment necessary.
Methadone	EFV	methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms. (R-methadone is the active form of methadone.)
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	ETR	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	sildenafil ↔	No dosage adjustment necessary.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Interactions			
Atovaquone/proguanil	EFV	↓ atovaquone AUC 75% ↓ progaunil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

[1] Approved dose for RPV is 25 mg once daily. Most pharmacokinetic interaction studies were performed using 75–150mg per dose.

Key to Abbreviations: ARV = antiretroviral, AUC = area under the curve, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, INR = international normalized ratio, MAC = *Mycobacterium avium* complex, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, OH-clarithromycin = active metabolite of clarithromycin, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, RPV = rilpivirine, RTV = ritonavir

Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents)
(Updated January 10, 2011)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Antivirals			
Ganciclovir Valganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible or closely monitor virologic response and hematologic toxicities.
Integrase Inhibitor			
RAL	TDF	RAL AUC ↑ 49%, C_{max} ↑ 64%	No dosage adjustment necessary
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, ZDV	No significant effect	No dosage adjustment necessary
Methadone	ABC	methadone clearance ↑ 22%	No dosage adjustment necessary
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44%	No dosage adjustment necessary
	ZDV	ZDV AUC ↑ 29%–43%	Monitor for ZDV-related adverse effects.
NRTIs			
ddI	d4T	No significant PK interaction	**Avoid coadministration**. Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48%–60%	**Avoid coadministration**.
Other			
Allopurinol	ddI	ddI AUC ↑ 113% ddI AUC ↑ 312% with renal impairment	**Contraindicated. Do not coadminister.** Potential for increased ddI-associated toxicities.
PIs			
ATV	ddI	With ddI-EC + ATV (with food): ddI AUC ↓ 34%; ATV no change	Administer ATV with food 2 hours before or 1 hour after didanosine.
	TDF	ATV AUC↓ 25% and C_{min} ↓ 23%–40% (higher C_{min} with RTV than without) TDF AUC ↑ 24%–37%	Dose: ATV/r 300/100 mg daily coadministered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C_{min} ↓ 30%, no change in AUC	Clinical significance unknown.
DRV/r	TDF	TDF AUC↑ 22%, C_{max} ↑ 24% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC ↓ 35%–44% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.
	ddI	ddI-EC ↓ 10% and TPV C_{min} ↓34% with TPV/r 1,250/100 mg BID	Separate doses by at least 2 hours.
	ZDV	ZDV AUC ↓ 31%–43% and C_{max} ↓ 46%–51% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.

Acronyms: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine.

Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs (Updated January 10, 2011)

This table provides information relating to pharmacokinetic interactions between MVC and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, please refer to **Table 16b**.

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungal			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Ketoconazole	MVC	MVC AUC ↑ 400%	Dose: MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Coadministration is not recommended. If coadministration is necessary use MVC 600 mg BID. If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Herbal Products			
St. John's wort	MVC	↓ MVC possible	Coadministration is not recommended.
Hormonal Contraceptives			
Hormonal contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	MVC	No data	

Acronyms: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CYP = cytochrome P, MVC = maraviroc

Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs
(Updated January 10, 2011)

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, C_{max} ↑ 315%, and C_{min} ↑ 46%	No dosage adjustment recommended
Antimycobacterials			
Rifabutin	RAL	RAL AUC ↑ 19%, C_{max} ↑ 39%, and C_{min} ↓ 20%	No dosage adjustment recommended
Rifampin	RAL	RAL AUC ↓ 40% and C_{min} ↓ 61% with RAL 400 mg Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: RAL 800 mg BID Monitor closely for virologic response.
Hormonal Contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	RAL	No significant effect	No dosage adjustment necessary

Acronyms: AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, RAL = raltegravir

Table 16a. Interactions Among PIs* (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

Drug Affected	ATV	FPV	LPV/r	RTV	SQV	TPV
DRV	Dose: ATV 300 mg once daily + DRV 600 mg BID + RTV 100 mg BID	No data	**Should not be coadministered because doses are not established**	Dose: (DRV 600 mg + RTV 100 mg) BID or (DRV 800 mg + RTV 100 mg) once daily	**Should not be coadministered because doses are not established**	No data
FPV	Dose: Insufficient data	•	**Should not be coadministered because doses are not established**	Dose: (FPV 1,400 mg + RTV 100 mg or 200 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID	Dose: Insufficient data	**Should not be coadministered because doses are not established**
LPV/r	Dose: ATV 300 mg once daily + LPV/r 400/100 mg BID	See LPV/r + FPV cell	•	LPV is coformulated with RTV as Kaletra.	See LPV/r + SQV cell	**Should not be coadministered because doses are not established**
RTV	Dose: (ATV 300 mg + RTV 100 mg) once daily	See RTV + FPV cell	LPV is coformulated with RTV as Kaletra.	•	Dose: (SQV 1,000 mg + RTV 100 mg) BID	Dose: (TPV 500 mg + RTV 200 mg) BID
SQV	Dose: Insufficient data	Dose: Insufficient data	Dose: SQV 1,000 mg BID + LPV/r 400/100 mg BID	See SQV + RTV cell	•	**Should not be coadministered because doses are not established**

Acronyms: ATV = atazanavir, BID = twice daily, DRV = darunavir, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, TPV = tipranavir

Table 16b. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors*, Maraviroc, Raltegravie, and Protease Inhibitors* (Updated October 14, 2011)

*DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV, IDV, and NFV drug interactions.

		EFV	ETR	NVP	RPV[1]	MVC	RAL
ATV	**PK data**	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300 mg + RTV 100 mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, C_{max} ↑ 47%, and C_{min} ↑ 58% ATV: AUC ↓ 17% and C_{min} ↓ 47% With (ATV 300 mg + RTV 100 mg) once daily ETR: AUC, C_{max}, and C_{min} ↑ approximately 30% ATV: AUC ↓ 14% and C_{min} ↓ 38%	With (ATV 300 mg + RTV 100 mg) once daily ATV: AUC ↓ 42% and C_{min} ↓ 72% NVP: AUC ↑ 25%	With boosted and unboosted ATV ↑ RPV possible	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300 mg + RTV 100 mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300 mg + RTV 100 mg) once daily RAL: AUC ↑ 41%
	Dose	**Do not coadminister with unboosted ATV.** In ART-naive patients (ATV 400 mg + RTV 100 mg) once daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister with ATV +/− RTV.**	**Do not coadminister with ATV +/− RTV.**	Standard	MVC 150 mg BID with ATV +/− RTV	Standard
DRV – always use with RTV	**PK data**	With (DRV 300 mg + RTV 100 mg) BID DRV: AUC ↓ 13%, C_{min} ↓ 31% EFV: AUC ↑ 21%	ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID DRV: no significant change ETR: AUC ↓ 37%, C_{min} ↓ 49%	With (DRV 400 mg + RTV 100 mg) BID DRV: AUC ↑ 24%[†2] NVP: AUC ↑ 27% and C_{min} ↑ 47%	RPV 150 mg once daily with (DRV 800 mg + RTV 100 mg) once daily DRV: no significant change RPV: AUC ↑ 130% and Cmin ↑ 178%	With (DRV 600 mg + RTV 100 mg) BID MVC: AUC ↑ 305% With (DRV 600 mg + RTV 100 mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600 mg + RTV 100 mg) BID RAL: AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Standard (ETR 200 mg BID) Despite decreased ETR, safety and efficacy established with this combination in a clinical trial	Standard	Standard	MVC 150 mg BID	Standard
EFV	**PK data**	•	↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	↓ RPV possible	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	MVC: 600 mg BID	Standard
ETR	**PK data**	↓ ETR possible	•	↓ ETR possible	↓ RPV possible	MVC: AUC ↓ 53%, C_{max} ↓ 60%	ETR: C_{min} ↓ 17% RAL: C_{min} ↓ 34%
	Dose	**Do not coadminister.**		**Do not coadminister**.	**Do not coadminister.**	MVC 600 mg BID	Standard
FPV	**PK data**	With (FPV 1,400 mg + RTV 200 mg) once daily APV: C_{min} ↓ 36%	With (FPV 700 mg + RTV 100 mg) BID APV: AUC ↑ 69%, C_{min} ↑ 77%	With unboosted FPV 1,400 mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 1,400 mg + RTV 100 mg) BID NVP: C_{min} ↑ 19%	With boosted and unboosted FPV ↑ RPV possible	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1,400 mg + RTV 300 mg) once daily or (FPV 700 mg + RTV 100 mg) BID EFV standard	**Do not coadminister with FPV +/− RTV.**	(FPV 700 mg + RTV 100 mg) BID NVP standard	Standard	MVC 150 mg BID	Standard
LPV/r	**PK data**	With LPV/r tablets 500/125 mg BID[‡3] + EFV 600 mg LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%	With LPV/r capsules LPV: AUC ↓ 27% and C_{min} ↓51%	RPV 150 mg once daily with LPV/r capsules LPV: no significant change RPV: AUC ↑ 52% and Cmin ↑ 74%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑153%	↓ RAL ↔ LPV/r
	Dose	LPV/r tablets 500/125 mg[‡] BID; LPV/r oral solution 533/133 mg BID EFV standard	Standard	LPV/r tablets 500/125 mg[3] BID; LPV/r oral solution 533/133 mg BID NVP standard	Standard	MVC 150 mg BID	Standard

Table 16b. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors*, Maraviroc, Raltegravir, and Protease Inhibitors*

		EFV	ETR	NVP	RPV[1]	MVC	RAL
NVP	**PK data**	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible	•	↓ RPV possible	No significant change	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**		**Do not coadminister.**	Without PI MVC 300 mg BID With PI (except TPV/r) MVC 150 mg BID	Standard
RAL	**PK data**	RAL: AUC ↓ 36%	ETR: C_{min} ↑ 17% RAL: C_{min} ↓ 34%	No data	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	No data	Standard	
RPV	**PK data**	↓ RPV possible	↓ RPV possible	↓ RPV possible	•	No data	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**		No data	No data
RTV	**PK data**	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100 mg BID RAL: AUC ↓ 16%
	Dose					MVC 150 mg BID	Standard
SQV - always use with RTV	**PK data**	With SQV 1,200 mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1,000 mg + RTV 100 mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, C_{min} ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With SQV 600 mg TID SQV: AUC ↓ 38% NVP: no significant change	↑ RPV possible	With (SQV 1,000 mg + RTV 100 mg) BID MVC: AUC ↑ 877% With (SQV 1,000 mg + RTV 100 mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100mg) BID	Standard	MVC 150 mg BID	Standard
TPV – always use with RTV	**PK data**	With (TPV 500 mg + RTV 100 mg) BID TPV: AUC ↓ 31%, C_{min} ↓ 42% EFV: no significant change With (TPV 750 mg + RTV 200 mg) BID TPV: no significant change EFV: no significant change	With (TPV 500 mg + RTV 200 mg) BID ETR: AUC ↓ 76%, C_{min} ↓ 82% TPV: AUC ↑ 18%, C_{min} ↑ 24%	With (TPV 250 mg + RTV 200 mg) BID and with (TPV 750 mg + RTV 100 mg) BID NVP: no significant change TPV: no data	↑ RPV possible	With (TPV 500 mg + RTV 200 mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500 mg + RTV 200 mg) BID RAL: AUC ↓ 24%
	Dose	Standard	**Do not coadminister.**	Standard	Standard	MVC 300 mg BID	Standard

1 Approved dose for RPV is 25mg once daily. Most pharmacokinetic interaction studies were performed using 75–150mg per dose.
2 Based on between-study comparison.
3 Use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

Key to Abbreviations: APV = amprenavir, AUC = area under the curve, ATV = atazanavir, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, DRV = darunavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV = lopinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV = saquinavir, TID = three times a day, TPV = tipranavir